Symptom persistence and biomarkers in post-COVID-19/chronic fatigue syndrome – results from a prospective observational cohort

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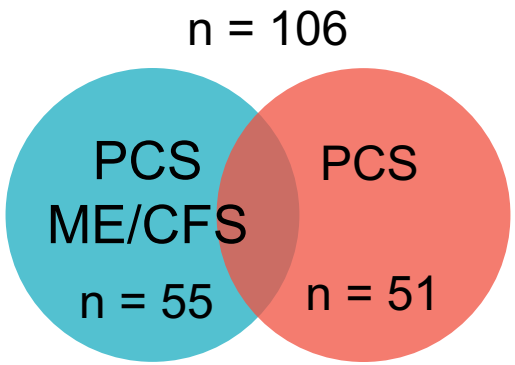
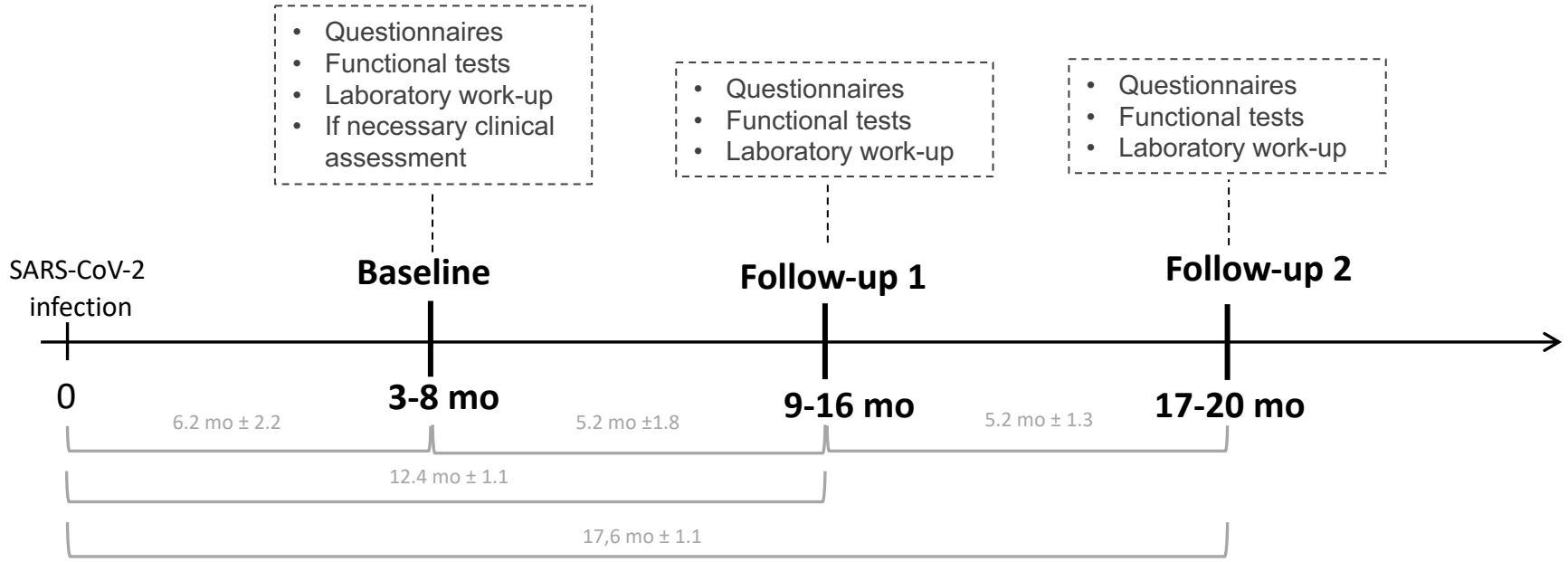
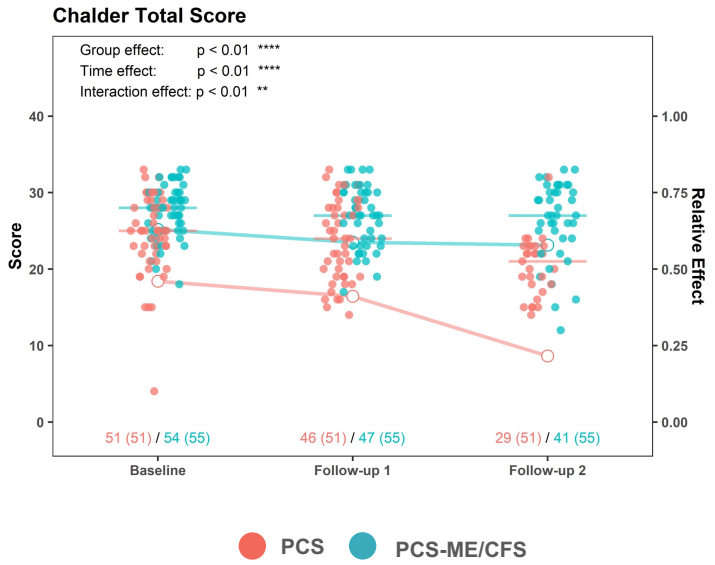
Methods and purpose

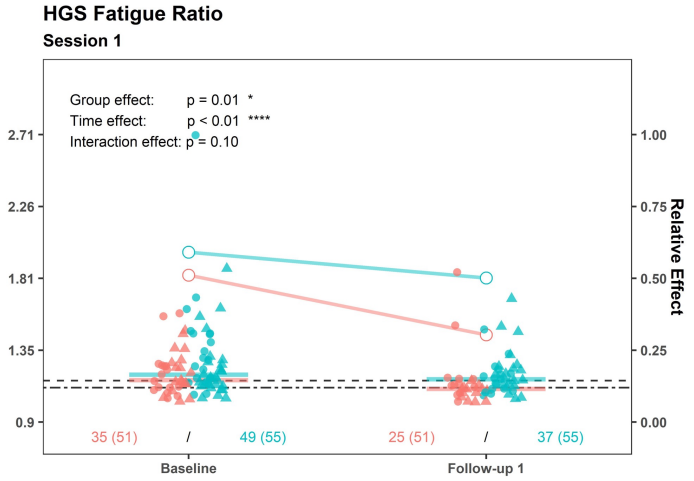


- Focus on PCS patients with moderate to severe fatigue
- Longitudinal evaluation of disease progression up to 20 months
- Broad clinical work-up

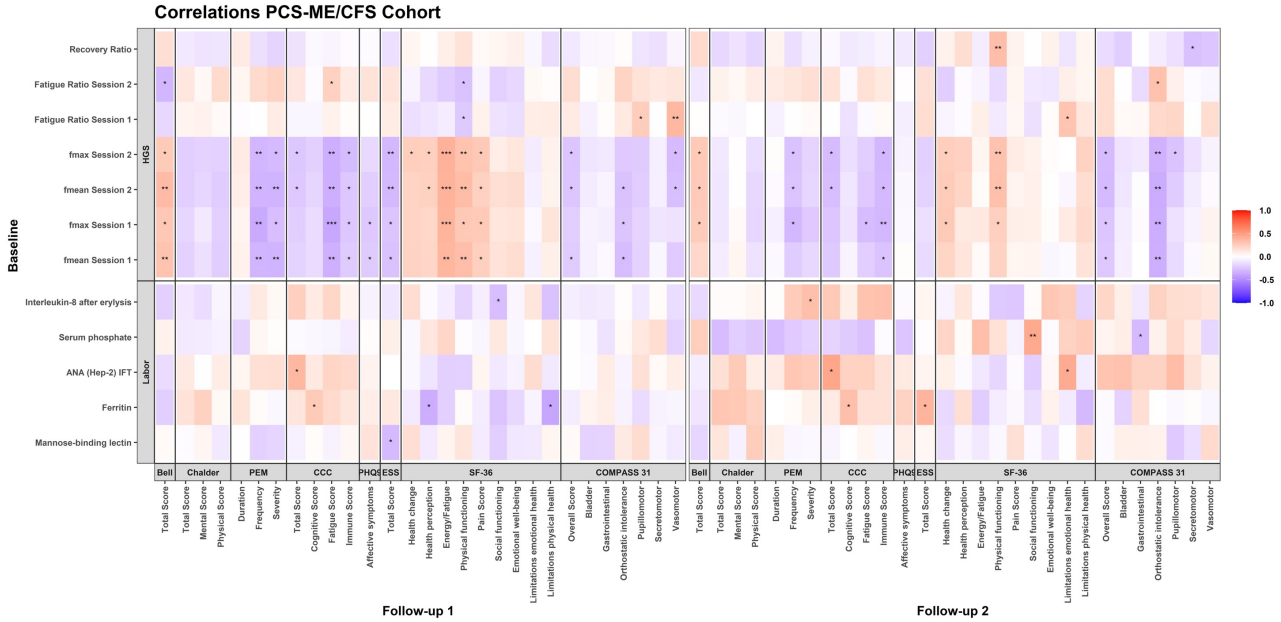


Results





- PCS can develop into the full scope of PCS-ME/CFS
- PCS-ME/CFS patients continue to be more affected, while PCS patients show clinical improvement
- The sub-classification of patients with post-COVID based on the CCC for ME/CFS is useful for further diagnostics and treatment
- Baseline HGS is linked to persisting disease severity, particularly in PCS-ME/CFS



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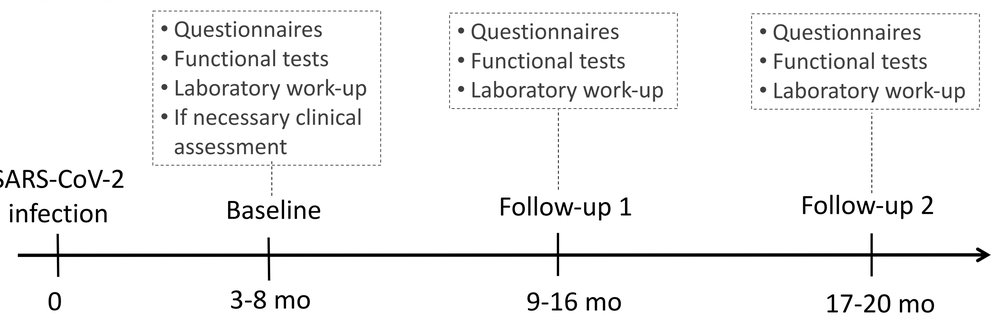
Introduction and Purpose

There is a worrying number of patients with various persistent symptoms following mild or moderate COVID-19 mainly presenting as fatigue, exertion intolerance, headache, myalgia, neurological and cognitive deficits as well as orthostatic disturbances, which can severely impact the patients' quality of life. Reports estimate a proportion of 2% to 10% of all COVID-19 patients to be still impaired one year after infection with SARS-CoV-2. While research has extensively focused on the acute phase of COVID-19 for a while now, long-term consequences of this viral disease have emerged as urgent medical problem with potentially great significance for those affected and many unanswered questions concerning pathomechanisms, prognosis and treatment.

We previously reported that a subset of PCS patients developed the full scope of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) 6 months after initial infection. Here we present the follow-up data up to 20 months after SARS-CoV-2 infection and describe biomarkers correlating with the disease course. We hypothesized that the subgroup of PCS-ME/CFS patients develops a chronic condition with distinct clinical and paraclinical features.

Methods

Figure 1



106 patients were included in the analysis, fulfilling the following inclusion criteria:

- (1) confirmed previous diagnosis of mild to moderate COVID-19 according to WHO criteria I or II,
- (2) persistent moderate to severe fatigue according to Chalder Fatigue Score (CFQ) and exertion intolerance with post exertional malaise (PEM),
- (3) absence of COVID-19-related organ dysfunction and
- (4) absence of preexisting fatigue or relevant cardiac, respiratory, neurological, or psychiatric comorbidities according to the European Network on ME/CFS (EUROMENE) guidelines.[1]

A subgroup of 55 patients fulfilled the Canadian Consensus Criteria (CCC) for ME/CFS and are referred to as PCS-ME/CFS; the remaining 51 patients are referred to as PCS.

Baseline assessment was conducted 3 to 8 months post COVID-19 manifestation. Follow-up visits were scheduled 9 to 16 months (follow-up 1) and 17 to 20 months (follow-up 2) post COVID-19 diagnosis.

Diagnosis and symptom assessment

We assessed symptom severity over time using standardized questionnaires: quantitative Canadian Consensus Criteria (qCCC), Bell Scale, Chalder Fatigue Score (CFQ), Short Form-36 (SF-36), Composite Autonomic Symptom Score 31 (COMPASS31) and Patient Health Questionnaire-9 (PHQ-9).

Functional tests and biomarker assessment

Postural tachycardia syndrome (POTS), orthostatic hypotension (OH) and diminished hand grip strength (HGS) were used as clinical markers to comprehensively characterize the broad variety of symptoms and their severity seen in PCS patients. Laboratory parameters were investigated, which have previously been associated with postinfectious fatigue syndromes including ferritin, interleukin in erythrocytes, mannose-binding lectin (MBL), antinuclear antibodies (ANAs) and serum phosphate (PO4).

Results and Conclusions

Figure 2

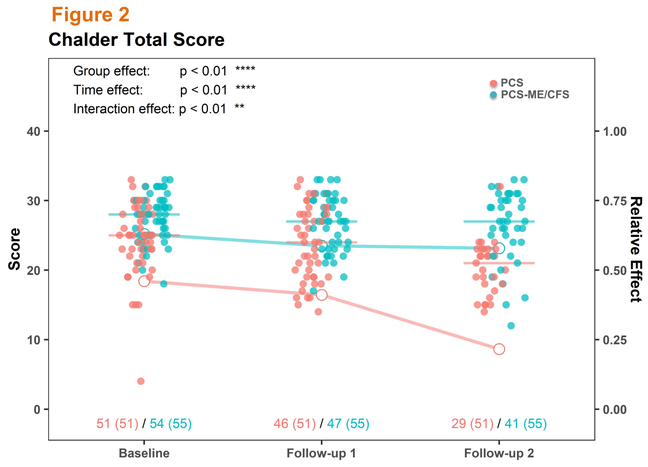


Fig. 2: Fatigue. Chalder Fatigue Total Score, ranging from 0 (no fatigue) to 33 (severe fatigue); Dots represent absolute score values (red for PCS, blue for PCS-ME/CFS) as quantified on the left Y axis. Bars depict group medians. Lines (red for PCS, blue for PCS-ME/CFS) depict main relative time, group, and interaction effects as quantified on the right Y axis.

By evaluating symptom severity over time, we found that patients fulfilling criteria for ME/CFS continued to be more affected than PCS patients by a wide range of symptoms including fatigue, physical disability, impaired social functioning, and emotional well-being. Exertion intolerance and post exertional malaise (PEM) as the hallmark of post-infectious fatigue syndromes remained more pronounced in PCS-ME/CFS up to 20 months after initial infection.

Figure 3

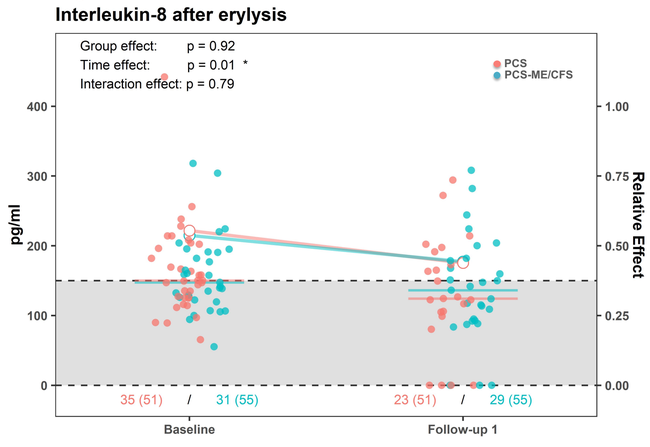


Fig. 3: Inflammatory biomarkers associated with postinfectious fatigue. Interleukin 8 (IL-8) after erylysis, reference <150 pg/ml. Dots represent absolute score values (red for PCS, blue for PCS-ME/CFS) as quantified on the left Y axis. Bars depict group medians. Lines (red for PCS, blue for PCS-ME/CFS) depict main relative time, group, and interaction effects as quantified on the right Y axis.

Our evaluation of biomarkers associated with post-infectious fatigue supports the presumption of ongoing inflammation in post-COVID-19. IL-8 was equally elevated in almost half of both patient cohorts at baseline and decreased significantly in both groups over time. Antinuclear antibodies (ANA) were detected in 25% (8/32) of PCS patients and 26% (8/30) PCS-ME/CFS patients at baseline without significant changes over time. 35% of all patients were deficient of PO4 at baseline, which is associated with increased mortality in COVID-19.[2]

Figure 4

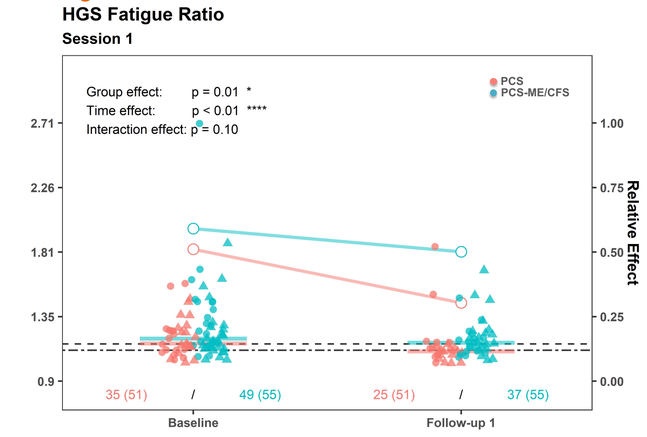


Fig. 4: Hand grip strength. Fatigue ratio (fmax/fmean) for session 1 for baseline and follow-up 1. Triangle data points depict patients <40 years. Age-dependent cut-offs are depicted according to Jäkel et al.[3] Red dots represent PCS cohort, blue dots PCS-ME/CFS cohort. Bars depict group medians with a 95% confidence interval.

HGS, a reliable parameter to quantify frailty and mortality, was evaluated (for female patients only to avoid gender bias) in two consecutive sessions at baseline and follow-up 1. The fatigue ratio (fmax/fmean) was determined for each session as a correlate for muscle fatigability with higher values indicating a stronger decline in force. PCS-ME/CFS patients showed higher fatigue ratios at baseline (session 2) and at follow-up (session 1) than PCS patients. We found HGS at baseline to be associated with disease severity at follow-up, particularly in the PCS-ME/CFS cohort, POTS was found only in PCS-ME/CFS patients.

Figure 5

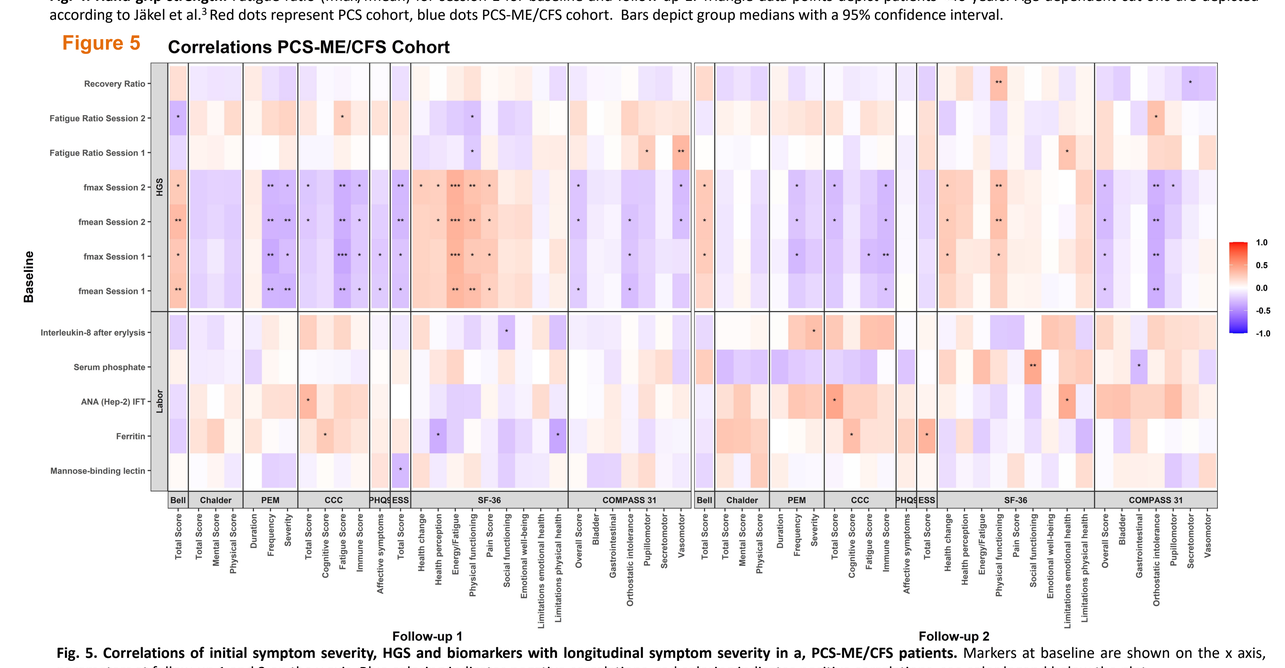


Fig. 5. Correlations of initial symptom severity, HGS and biomarkers with longitudinal symptom severity in a, PCS-ME/CFS patients. Markers at baseline are shown on the x axis, parameters at follow-up 1 and 2 on the y axis. Blue coloring indicates negative correlations, red coloring indicates positive correlations, see color legend below the plot

We concluded that the post-COVID condition can develop into the full scope of the post-infectious fatigue syndrome (PCS-ME/CFS) based on the Canadian Consensus Criteria (CCC). Thus, the sub-classification of patients with post-COVID based on the CCC for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is useful for further diagnostics and treatment.

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Acknowledgements and Disclosures

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